

MEDIA & INVESTOR RELEASE

Novartis announces new Mayzent® (siponimod) data show sustained effect in delaying disability for up to five years in patients with secondary progressive multiple sclerosis (SPMS)

- *New long-term data from EXPAND show patients with SPMS continuously treated with Mayzent® (siponimod) experienced lower risk of disability progression and cognitive decline than patients who delayed Mayzent treatment¹*
- *Separate post-hoc analysis from EXPAND demonstrated Mayzent reduced cortical grey matter (cGM) and thalamic atrophy in patients with SPMS², outcomes associated with long-term irreversible disability accumulation³*
- *Mayzent is the first and only oral disease modifying therapy (DMT) studied and proven to delay disability progression in a broad range of SPMS patients*

Basel, April 21, 2020 — Novartis announced today new Mayzent® (siponimod) data in the April supplemental issue of *Neurology*®, the medical journal of the American Academy of Neurology. The data build on existing clinical evidence that Mayzent has proven to slow physical disability progression and provide cognitive benefits in people living with secondary progressive multiple sclerosis (SPMS)¹. Although every patient's multiple sclerosis (MS) journey is unique, 1 in 4 relapsing-remitting MS (RRMS) patients on treatment transition to SPMS within 10 years of RRMS onset*⁴.

Data released from the five-year EXPAND open-label extension trial assessed the long-term efficacy and safety of Mayzent in patients with SPMS who on entering the extension trial either continued on Mayzent treatment (Mayzent group) or switched from placebo to Mayzent (placebo switch group). Patients in the Mayzent group were significantly less likely to experience both three- and six-month confirmed disability progression (CDP) (p=0.0064 and p=0.0048, respectively) compared with the placebo switch group, which underscores advantages of early treatment initiation¹. These data were included in the April supplemental issue of *Neurology* after the 2020 American Academy of Neurology Annual Meeting was cancelled due to COVID-19.

“The data continue to show that Mayzent has the ability to help patients maintain independence for longer through its long-term effect on delaying progression and cognitive impairment,” said Norman Putzki, MD, Global Head of Development Neuroscience. “Novartis is committed to reimagining medicine for patients with progressive diseases and with Mayzent, Novartis offers patients hope for improved health outcomes.”

The new data also show a 52% reduction in the annualized relapse rate (ARR) observed in the Mayzent group compared to the placebo switch group ($p < 0.0001$). Risk of confirmed worsening of cognitive impairment (according to the Symbol Digit Modalities Test) at six-months was reduced by 23% for the Mayzent group compared with placebo switch group ($p = 0.0014$). The benefits seen in the Mayzent group were sustained for up to five years, underscoring the advantages of early treatment initiation with Mayzent. The incidence of adverse events was consistent with the controlled treatment period¹. This EXPAND open-label extension is ongoing for up to a total of seven years.

Additional Mayzent data shared in the same *Neurology* issue includes a new post-hoc analysis from EXPAND, which showed Mayzent consistently reduced cortical grey matter (cGM) and thalamic atrophy in patients with SPMS, including those with less active and more advanced disease. Across the subgroups studied, Mayzent reduced cGM atrophy versus placebo by 48–116% ($p < 0.01$ at both M12 and M24) and thalamic atrophy by 30–68% ($p < 0.05$ at both M12 and M24; except for ‘disease duration >15 years’ $p = 0.1029$ at M12)². Combined with other analyses, these findings could translate into a favorable impact on long-term clinical outcomes including disability progression and cognitive decline.

Further analysis from EXPAND, evaluating Mayzent’s effect on magnetization transfer ratio (MTR) changes in patients with SPMS, builds on existing pre-clinical evidence that suggests Mayzent may promote repair mechanisms in the central nervous system (CNS). MTR is a technique widely used for estimating myelin content in the brain. MTR results show that Mayzent significantly reduces de-myelination and substantiate previous pre-clinical findings on remyelination⁵.

“These data highlight the critical importance of early treatment intervention with a disease-modifying treatment, such as Mayzent, to ensure the best possible long-term outcomes for patients with MS who are experiencing progression,” said Bruce Cree, MD, PhD, MAS, Clinical Research Director and George A. Zimmermann Endowed Professor in Multiple Sclerosis, University of California, San Francisco, School of Medicine. “It’s never too early to stay ahead of progression in multiple sclerosis, since the early identification of physical and cognitive changes – even subtle ones – can indicate MS disease progression and therefore allow for timely intervention.”

**For specific indications of Mayzent approved in each country, see the section “About Mayzent® (siponimod)” below.*

†As measured by prolonged time to wheelchair dependence for patients with SPMS by an average of 4.3 years versus placebo.

‡Clinically isolated syndrome (CIS) is defined as a first episode of neurologic symptoms that lasts at least 24 hours and is caused by inflammation or demyelination in the central nervous system⁶.

About the EXPAND Study⁷

EXPAND is a randomized, double-blind, placebo-controlled Phase III study, comparing the efficacy and safety of Mayzent versus placebo in people with SPMS with varying levels of disability (Core Part), EDSS scores of 3.0–6.5, followed by extended treatment with open-label BAF312 to obtain data on long-term safety, tolerability and efficacy (Extension Part)⁸. It is the largest randomized, controlled study in SPMS to date, including 1,651 people with a diagnosis of SPMS from 31 countries. Mayzent demonstrated a safety profile that was overall consistent with the known effects of S1P receptor modulation. It reduced the risk of three-month CDP by a statistically significant 21% ($p = 0.013$; primary endpoint). CDP was defined as a 1-point increase in EDSS, if the baseline score was 3.0–5.0, or a 0.5-point increase, if the baseline score was 5.5–6.5. No significant differences were found in the Timed 25-Foot Walk Test. T2 lesion volume was reduced by 79% as compared to placebo. Additional secondary endpoints included a relative reduction in the ARR by 55%, and compared to placebo, more patients were free from Gd-enhancing lesions (89% vs 67% for placebo) and from new or enlarging T2 lesions (57% vs 37% for placebo). Additional exploratory analyses presented at the 35th Congress of the European Committee for Treatment and Research in

Multiple Sclerosis (ECTRIMS), demonstrated Mayzent can help patients keep their mobility for over four years longer on average^{9†}.

About Mayzent® (siponimod)

Mayzent is a sphingosine 1-phosphate receptor modulator that selectively binds to S1P1 and S1P5 receptors. In relation to the S1P1 receptor, it prevents the lymphocytes from egressing the lymph nodes and as a consequence, from entering the CNS of patients with MS⁷. This leads to the anti-inflammatory effects of Mayzent¹⁰. Mayzent also enters the CNS and binds to the S1P5 sub-receptor on specific cells in the CNS^{11,12,13}, including astrocytes and oligodendrocytes and has shown pro-remyelinating and neuroprotective effects in preclinical models of MS^{14,15,16}.

In the European Union (EU), Mayzent is indicated for the treatment of adult patients with SPMS with active disease evidenced by relapsing or imaging features of inflammatory activity. In the US, Mayzent is approved for the treatment of relapsing forms of MS, to include clinically isolated syndrome (CIS[†]), relapsing remitting disease and active secondary progressive disease in adults. The approvals are based on the Phase III EXPAND trial, the largest controlled clinical study of a broad range of SPMS patients, showing Mayzent significantly reduced the risk of disease progression, including impact on physical disability and cognitive decline⁷. Mayzent is also approved in Australia and Albania for adult patients with SPMS and in Canada and United Arab Emirates for adult patients with active SPMS. Novartis is committed to bringing Mayzent to patients worldwide, and additional regulatory filings are currently underway in Switzerland, Japan, China, and elsewhere.

About Multiple Sclerosis

MS disrupts the normal functioning of the brain, optic nerves and spinal cord through inflammation and tissue loss¹⁷. MS, which affects approximately 2.3 million people worldwide¹⁸, is often characterized into three forms: primary progressive MS (PPMS)¹⁹, RRMS, and SPMS, which follows from an initial RRMS course and is characterized by physical and cognitive changes over time, in presence or absence of relapses, leading to a progressive accumulation of neurological disability²⁰. Approximately 85% of patients initially present with relapsing forms of MS¹⁸. There remains a high unmet need for safe and effective treatments to help delay disability progression in SPMS with active disease (with relapses and/or evidence of new MRI activity)²⁰.

About Novartis in MS

In addition to Mayzent, the Novartis MS portfolio includes also Gilenya® (fingolimod, an S1P modulator), which is indicated in the EU for the treatment of adult patients and children and adolescents 10 years of age and older with RRMS. In the United States, Gilenya is approved for the treatment of adults and pediatric patients aged 10 years and older with RMS, to include CIS, relapsing remitting disease and active secondary progressive disease.

Ofatumumab (OMB157), a fully human anti-CD20 monoclonal antibody (mAb) that targets B-cells, is in development for treating RMS. Positive Phase III data presented in September 2019 show ofatumumab met primary endpoints to reduce the ARR in patients with RMS²¹. If approved, ofatumumab will potentially become a treatment for a broad RMS population and the first subcutaneous B-cell therapy that can be self-administered at home.

Extavia® (interferon beta-1b for subcutaneous injection) is approved in the US for RMS, to include CIS, relapsing remitting disease and active secondary progressive disease. In Europe, Extavia is approved to treat people with RRMS, SPMS with active disease and people who have had a single clinical event suggestive of MS.

In the US, the Sandoz Division of Novartis markets Glatopa® (glatiramer acetate injection) 20mg/mL and 40mg/mL, generic versions of Teva's glatiramer acetate.

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This press release contains forward-looking statements within the meaning of the United States Private Securities Litigation Reform Act of 1995. Forward-looking statements can generally be identified by words such as “potential,” “can,” “will,” “plan,” “may,” “could,” “would,” “expect,” “anticipate,” “seek,” “look forward,” “believe,” “committed,” “investigational,” “pipeline,” “launch,” or similar terms, or by express or implied discussions regarding potential marketing approvals, new indications or labeling for the investigational or approved products described in this press release, or regarding potential future revenues from such products. You should not place undue reliance on these statements. Such forward-looking statements are based on our current beliefs and expectations regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. There can be no guarantee that the investigational or approved products described in this press release will be submitted or approved for sale or for any additional indications or labeling in any market, or at any particular time. Nor can there be any guarantee that such products will be commercially successful in the future. In particular, our expectations regarding such products could be affected by, among other things, the uncertainties inherent in research and development, including clinical trial results and additional analysis of existing clinical data; regulatory actions or delays or government regulation generally; global trends toward health care cost containment, including government, payor and general public pricing and reimbursement pressures and requirements for increased pricing transparency; our ability to obtain or maintain proprietary intellectual property protection; the particular prescribing preferences of physicians and patients; general political, economic and business conditions, including the effects of and efforts to mitigate pandemic diseases such as COVID-19; safety, quality, data integrity or manufacturing issues; potential or actual data security and data privacy breaches, or disruptions of our information technology systems, and other risks and factors referred to in Novartis AG’s current Form 20-F on file with the US Securities and Exchange Commission. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

About Novartis

Novartis is reimagining medicine to improve and extend people’s lives. As a leading global medicines company, we use innovative science and digital technologies to create transformative treatments in areas of great medical need. In our quest to find new medicines, we consistently rank among the world’s top companies investing in research and development. Novartis products reach nearly 800 million people globally and we are finding innovative ways to expand access to our latest treatments. About 109,000 people of more than 145 nationalities work at Novartis around the world. Find out more at <https://www.novartis.com>.

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References

1. Kappos L, et al. Long-term Efficacy and Safety of Siponimod in Patients with SPMS: EXPAND Extension Analysis up to 5 Years. *Neurology*. 2020; 94 (15 Supplement).
2. Fox R, et al. Siponimod Reduces Grey Matter Atrophy in Patients with Secondary Progressive Multiple Sclerosis: Subgroup Analyses from the EXPAND study. *Neurology*. 2020; 94 (15 Supplement).
3. D.L. Arnold, et al. Relationship between grey matter atrophy, disability and cognition in patients with secondary progressive multiple sclerosis: analysis from the EXPAND study. 35th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), September 2019.
4. Khurana V, et al. Time to, and rate of secondary progression in patients with multiple sclerosis: results of a systematic search. 7th Joint Congress of the European Committee for Treatment and Research in Multiple Sclerosis-Americas Committee for Treatment and Research in Multiple Sclerosis, October 2017.
5. D.L. Arnold, et al. Magnetization Transfer Imaging in Secondary Progressive Multiple Sclerosis Patients Treated with Siponimod: Results from the Phase III EXPAND Study. *Neurology*. 2020; 94 (15 Supplement).

6. National MS Society. Clinically Isolated Syndrome (CIS). [https://www.nationalmssociety.org/Symptoms-Diagnosis/Clinically-Isolated-Syndrome-\(CIS\)](https://www.nationalmssociety.org/Symptoms-Diagnosis/Clinically-Isolated-Syndrome-(CIS)). Accessed April 2020.
7. Kappos L, Cree B, Fox R, et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomized, phase 3 study. *Lancet*. Published online March 22, 2018. [http://dx.doi.org/10.1016/S0140-6736\(18\)30475-6](http://dx.doi.org/10.1016/S0140-6736(18)30475-6).
8. ClinicalTrials.gov. Exploring the Efficacy and Safety of Siponimod in Patients With Secondary Progressive Multiple Sclerosis (EXPAND). <https://clinicaltrials.gov/ct2/show/NCT01665144>. Accessed April 2020.
9. Vermersch P, Gold R, Kappos L, et al. Siponimod Delays the Time to Wheelchair in Patients with SPMS: Results from the EXPAND study. 35th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), September 2019.
10. Gergely P, Nuesslein-Hildesheim B, Guerini D, et al. The selective sphingosine 1-phosphate receptor modulator BAF312 redirects lymphocyte distribution and has species-specific effects on heart rate. *Brit J Pharm*. 2012; 167:1035-47.
11. Tavares A, Barret O, Alagille D, et al. Brain distribution of MS565, an imaging analogue of siponimod (BAF312), in non-human primates. *Eur J Neurol*. 2014;21 (Suppl 1):504-PP2067.
12. Briard E, Rudolph B, Desrayuad S, et al. MS565: A SPECT tracer of evaluating the brain penetration of BAF312 (siponimod). *Chem Med Chem*. 2015; 10(6):1008-18.
13. Bigaud M, Perdoux J, Ramseier P et al. Pharmacokinetic/Pharmacodynamic Characterization of Siponimod (BAF312) in Blood versus Brain in Experimental Autoimmune Encephalomyelitis Mice. *Neurology*. 2019;P2.2-066.
14. Mannioui A, Vauzanges Q, Fini JB, et al. The *Xenopus* tadpole: An in vivo model to screen drugs favoring remyelination. *Mult Scler*. 2018;24(11):1421-32.
15. Martin E, Urban B, Beerli C, et al. Siponimod (BAF312) is a potent promyelinating agent: preclinical mechanistic observation. P1376. 35th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, September 2019.
16. Dietrich M, Hecker C, Ramseier P, et al. Neuroprotective potential for siponimod (BAF312) revealed by visual system readouts in a model of experimental autoimmune encephalomyelitis-optic neuritis (EAEON). P844. 35th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, September 2019.
17. National Multiple Sclerosis Society. Definition of MS. <https://www.nationalmssociety.org/What-is-MS/Definition-of-MS>. Accessed April 2020.
18. Multiple Sclerosis International Federation. Atlas of MS 2013. <http://www.msif.org/wp-content/uploads/2014/09/Atlas-of-MS.pdf>. Accessed April 2020.
19. MS Society. Types of MS. <https://www.mssociety.org.uk/about-ms/types-of-ms>. Accessed April 2020.
20. National Multiple Sclerosis Society. Secondary Progressive MS (SPMS). <https://www.nationalmssociety.org/What-is-MS/Types-of-MS/Secondary-progressive-MS>. Accessed April 2020.
21. Hauser S. Efficacy and safety of ofatumumab versus teriflunomide in relapsing multiple sclerosis: results of the phase 3 ASCLEPIOS I and II trials. Oral presentation. ECTRIMS 2019.

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